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P2Y12 receptor inhibitors in patients with non-ST-elevation acute coronary syndrome in the real world: use, patient selection, and outcomes from contemporary European registries.

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P2Y12 receptor inhibitors in patients with non-ST-elevation acute coronary syndrome in the real world: use, patient selection, and outcomes from contemporary European registries

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Abstract

Non-ST-elevation acute coronary syndrome (NSTE-ACS) is present in about 60-70 % of patients admitted with acute coronary syndromes in clinical practice. This study provides an overview on patient characteristics, dual antiplatelet therapy (DAPT) and outcomes at discharge from hospital up to 1 year in these patients in real life. A total of 10 registries (comprising 84054 NSTE-ACS patients) provided data in a systematic manner on patient characteristics and outcomes of NSTE-ACS in general, and 6 of those (with 52173 NSTE-ACS patients) also by P2Y12 receptor inhibitor. In the unadjusted analysis there were substantial differences between registries in terms of study setting, eligibility of patients, site selection and definition of endpoints including bleeding events.

All-cause death rates across registries ranged from 0.76% to 4.79% in-hospital (based on data from 84053 patients for this time point); from 1.61% to 6.65% at 30 days; from 3.66% to 7.16% at 180 days; and from 3.14% to 9.73% at 1 year. Major bleeding events were reported in up to 2.77% in hospital (in 7 registries), in up to 1.08% at 30 days (data from one registry only), and in 2.06% at 1 year (one registry). There were substantial differences in the use and patient selection for clopidogrel, prasugrel and ticagrelor, which were associated with differences in short- and long-term ischaemic and bleeding events. In future registries data collection should be performed in a more standardized way with respect to endpoints, definitions, and time points.

218 words

Key words

Acute coronary syndromes, non-ST-segment elevation, observational, antiplatelets, P2Y12 receptor inhibitors, clopidogrel, prasugrel, ticagrelor

BACKGROUND

Antiplatelet therapy is recommended in all patients with ACS regardless of their revascularization strategy. The current guidelines of the European Society of Cardiology (ESC) on the management of patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) recommend aspirin for all patients without contraindications at an initial oral loading dose of 150-300 mg, and at an oral maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.[1] Further, as part of dual antiplatelet therapy (DAPT), a P2Y12 receptor inhibitor should be added to aspirin and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding (Class I level A recommendation). Prasugrel as 60 mg loading dose followed by 10 mg/d maintenance dose is recommended in patients who are proceeding to PCI if there is no contraindication (Class I level B), but not in patients in whom coronary artery anatomy is not known (Class III level B). Ticagrelor as 180 mg loading dose followed by 90 mg twice daily is recommended in the absence of contraindications for all patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy and including those pre-treated with clopidogrel (Class I level B). Finally, clopidogrel as 300- to 600 mg loading dose followed by 75 mg daily maintenance dose is recommended for patients who cannot receive ticagrelor or prasugrel or require oral anticoagulation (Class I level B).[1] Because prasugrel and ticagrelor have higher antithrombotic potency and proven superiority in outcome trials, (as in STEMI) these drugs are preferred over clopidogrel for patients presenting with NSTE-ACS.[7]

Registries and other observational studies are an important source of information on the efficacy and safety of medication under clinical practice conditions. The “Platelet Inhibition Registry in ACS EvalUation Study” (acronym PIRAEUS) group convened consisting of owners or principal investigators of national or multinational European ACS registries.[2] The initiative aims to integrate the wide array of data generated by individual European ACS registries to gain a comprehensive overview on efficacy and safety of the P2Y12 receptor inhibitors used for the treatment of this condition. We have described the participating registries in a narrative and tabular form in detail in an earlier review,[2] and also provided an overview on the outcomes of STEMI patients.[3]

This report presents data of NSTE-ACS patients in various European registries, with focus on the use, patient selection and outcomes of P2Y12 receptor inhibitor-based DAPT.

METHODS

In order to obtain a comprehensive overview on appropriate registries the following selection criteria were applied: European multicentre or single-centre observational studies on real-life experience in the management of ACS within the last 5 years; large unselected patient cohorts; data on PCI; data on management during initial hospitalisation for ACS available; follow-up data on outcomes (death, cardiac events, bleedings) available; previous publication of data in peer-reviewed journals and/or reporting of unpublished data, with information on outcomes of drug treatment of patients with P2Y12 receptor inhibitors at least until discharge from the hospital; willingness of registry owners to take part in PIRAEUS and share data.

Of the registries fulfilling the above criteria and whose owners were contacted, a total of 17 registries were analysed. They are described in detail in a recent review paper including setting, aims and scope, and selected baseline characteristics of the included patients.[2]

Registry owners were asked to provide detailed current data on (a) the full ACS cohort as well as for the STEMI and NSTE-ACS groups separately (irrespective of treatment) and (b) subgroups of patients treated with the P2Y12 receptor inhibitors prasugrel, ticagrelor or clopidogrel. Only aggregate data in tabular format were received, as the pooling of per patient data was not covered by patients' informed consent and/or was not possible due to ownership of data issues. The data collection sheet specified time points at discharge from hospital, at 30 days, at 180 days and at 1 year. Endpoints of interest comprised all-cause death, cardiovascular death, stroke, recurrent myocardial infarction, and repeat PCI (for efficacy), and life-threatening/major and minor bleeding (for safety). For bleeding events, the definition used by each registry was requested from the registry owners, but was not always available or sometimes had changed during the time of the registry data collection.

Registry owners were asked to provide percentages for the various events together with event number and patient number at the various time points. Data were not adjusted nor weighted.

Statistical analysis

For the current paper, patients with NSTE-ACS diagnosis at admission were selected for analysis. Patients from 10 registries were included for statistical analysis. The patient numbers were used by a statistician to calculate event rates for the total cohort and by DAPT regimen, respectively, with two-sided 95% confidence intervals (CI) using the Clopper-Pearson interval. Cohorts comprising fewer than 100 patients were excluded from analyses because of the small number of events. Event rates and 95% CIs for each cohort were shown using forest plots.

Bubble plots were used to confirm the relationships between age and event rates whereby the size of the bubble depended on the patient numbers of the respective subgroup. These analyses were sent to the individual registry holders for them to confirm the data, enter corrections, and, if indicated, provide additional data.

A description of the registries that provided NSTE-ACS data is in the online supplement, part 1.

Online supplement

ACS REGISTRIES THAT PROVIDED DATA ON NSTE-ACS PATIENTS FOR THE CURRENT EFFECTIVENESS AND SAFETY ANALYSES

AAPCI and ADAPT (Austria). The Austrian Acute PCI registry (AAPCI) is a nationwide, prospective, multicentre, observational registry of interventional reperfusion therapy in acute myocardial infarction. Since its implementation in 2005, it evaluates interventional therapy and determines predictors of successful treatment and in-hospital outcome in patients receiving coronary intervention in a real-world setting of AMI.[4] Patients are eligible for documentation if they were admitted with AMI to one of the participating centres within 24 h (STE-ACS) or 72h (NSTE-ACS) of symptom onset.

The registry collects data on demographics, cardiac history with previous coronary intervention and previous MI, mode of admission, key time points and intervals to describe the event and intervention, the intervention itself together with drug treatment details, and the outcomes. Data from the registry allow a comparison of the outcomes of STEMI or NSTE-ACS treatment with each of the three available P2Y12 receptor inhibitors.

The Austrian Dual Antiplatelet Therapy Registry ADAPT is a sub-registry established to specifically address effectiveness and safety of ticagrelor and prasugrel in real-world PCI in ACS.

AMIS Plus (Switzerland). The Acute Myocardial Infarction in Switzerland (AMIS) registry was started in 1997 to prospectively collect real-life data on STEMI and NSTE-ACS patients.[5] In 2000 it was renamed AMIS Plus after the extension to patients with unstable angina (UA). In that cohort, 3.2% of all NSTEMI patients had UA.

Since 2005, a subset of hospitals also collects follow-up information on about half of the ACS patients 1 year after hospital discharge via telephone interviews and questionnaires. Participating hospitals include all types from regional to large tertiary centres. In 2010, out of 106 hospitals in Switzerland treating ACS patients 76 temporarily or continuously contributed patients to AMIS Plus.

The data from the AMIS Plus registry are used to characterise examination and treatment strategies of patients with acute myocardial infarction and UA, to assess compliance with guidelines, and to guide the optimization of interventions.

The data of the registry allow for a direct comparison of the outcomes of the DAPT for all three P2Y12 receptor inhibitors; however, in the NSTE-ACS group, the number of patients treated with prasugrel is about four times lower than the number of patients treated with clopidogrel. To date, the registry collected data from more than 51,000 patients.

ATACS (Germany). The ATACS (Antithrombotic Therapy in patients with Acute Coronary Syndrome) registry is a sub-registry of the ALKK coronary angiography and PCI registry. For the ATACS registry in the 30 participating hospitals between October 2009 and February 2013 specific information on timing and dosing of clopidogrel and prasugrel, risk factors for bleeding complications and timing and outcome of bleedings were added to the standard questionnaire. The registry focussed on ACS patients and the results of the STEMI patients scheduled for primary PCI, receiving a loading dose of either clopidogrel or prasugrel.[6]

BLITZ-4 (Italy). The "Blitz-4 Qualita'" project was initiated in 2009 and includes 163 Italian Coronary Care Units (CCUs). The goal of the project was to prospectively collect demographics, process of care and outcome measures among patients with ACS (STEMI or NSTE-ACS), to provide feedback to participating centres as well as specific interventions aimed at increasing compliance with the guidelines, and, ultimately, to improve the quality and standardization of myocardial infarction care. For this reason two enrolment phases were selected (September-November 2009 and February-April 2010), each followed by a feedback of both local and general performance.

Overall, 5854 patients with STEMI and 5852 patients with NSTE-ACS were consecutively enrolled. Data collection included pharmacological and non-pharmacological indicators of performance as well as measure of excess dose of antithrombotic drugs in eligible populations. Outcome measures during the in-hospital stay, at 30 days[7] and at 6 months[8] were also collected. An outcome comparison between the P2Y12 receptor inhibitors was not performed as no patients received prasugrel or ticagrelor.

CZECH-2 (Czech Republic). CZECH-2 was a prospective multicentre, observational, regional survey performed in 2012, in which all 28 hospitals without catheterization availability and all 4 cardiology centres with non-stop PCI service in the 4 Czech counties (out of 14 existing counties) participated (100% hospitals in participating regions). [9] The registry documented all consecutive STEMI, NSTEMI and UA. Patients were treated with prasugrel or clopidogrel, but not ticagrelor (not available in the Czech Republic at the time of registry initiation).

DIOCLES (Spain). DIOCLES study is a prospective, multicentre, registry in Spain, which documented STEMI, NSTEMI, and UA patients limited to a documentation period in 2012 and a 6-month follow-up.[10] Except for pre-hospital ACS treatment, the registry summarises all details of enrolled patients, including complete clinical histories and comorbidities. The DIOCLES registry documents outcomes for DAPT treatment with clopidogrel or prasugrel, however, the size of the prasugrel group is a tenth of the clopidogrel group and is therefore not reported in detail in this review.

FAST-MI (France). FAST-MI ("French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction") is part of a programme implementing nationwide one-month surveys carried out every 5 years, since 1995. [11, 12] All types of institutions are eligible for participation (i.e., university hospitals, public hospitals, military hospitals, or private clinics, with or without on-site catheterization facilities). Several surveys were carried out, with a cohort recruited in 2010 (reported in this paper), and the next cohort recruited at the end of 2015.

Patients were eligible for documentation if they had STEMI or NSTEMI, but not UA, and if they were admitted alive to the coronary care unit or intensive care unit within 48 hours of symptom onset.

Newcastle-upon-Tyne dataset (UK). The Newcastle dataset is not a typical registry, but a retrospective analysis of prospectively collected data of the Freeman Hospital, Newcastle-upon-Tyne, in the Northeast of England.[13] Freeman Hospital is a regional tertiary centre serving a population of approximately 2 million and performing over 850 primary PCI cases per year. Cases from 2010 to 2013 are reported, however, without comparisons of different DAPT regimens.

SCAAR (Sweden). SCAAR (Swedish Coronary Angiography and Angioplasty Registry) is a prospective multicentre registry, which since 1990 documents all consecutive coronary angiographies and PCI procedures performed in Sweden.[14] Data from SCAAR are reported annually.[15] The registry covers all regions of Sweden and all 29 hospitals with a catheterization laboratory and enrols STEMI, NSTEMI and UA patients (in addition to angiography performed for any other reason). Data on all three P2Y12 receptor inhibitors are available. The NSTEMI dataset reported in this paper does not include UA patients.

SPUM-ACS (Switzerland). The SPUM-ACS (Special Program University Medicine-Acute Coronary Syndromes) research network collects data since 2009 on a prospective cohort of

patients hospitalised for an ACS in 4 university medical centres in Switzerland (Bern, Geneva, Lausanne and Zurich). [16] It includes STEMI, NSTEMI, UA and elective stable angina patients.

In Cohort 1 (recruited between 9/2009 and 10/2012), as per protocol and according to the ESC Guidelines, patients were treated with DAPT after PCI with clopidogrel (NSTE-ACS, STEMI <60 kg or >75 years or history of TIA or stroke) or prasugrel/ticagrelor (other STEMIs).[17] Treatment details in hospital were not provided, but outcomes of treatment with all three P2Y12 receptor inhibitors were compared.

End of Online supplement

Results

In total, 10 registries provided specific information about NSTE-ACS patients (Table 1). Of these, 6 provided specific data on P2Y12 DAPT (AAPCI/ADAPT, AMIS Plus, ATACS, DIOCLES, SCAAR, and SPUM). All reported data on clopidogrel, 5 on prasugrel (all with the exception of DIOCLES), and 3 on ticagrelor (AAPCI/ADAPT, AMIS Plus, SCAAR). The remaining 4 registries (BLITZ-4, CZECH-2, FAST-MI, Newcastle) only had data on NSTE-ACS patients overall, but no data on P2Y12 treatment groups.

Characterisation of the NSTE-ACS cohorts

Total patient number ranged between 586 patients (CZECH-2) and 52319 (SCAAR). Mean patient age in the registries varied between 65 years (AAPCI, SPUM, Newcastle) and 70 years (CZECH-2), with the other registries in between. Males were more frequent than women in all registries. Diabetes mellitus was frequently noted as comorbidity, in the range of 18.9% (Newcastle 2010) to 40.5% (CZECH-2). The prevalence of previously diagnosed coronary artery disease varied substantially from 28.6% (SCAAR) to 100% (ATACS, with this rate due to the fact that CAD was an inclusion criterion) and prior myocardial infarction rates ranged from 17% (AAPCI) to 30.2% (Newcastle 2012). Prior stroke was noted in a range from 2.7% (SPUM) to 9.4% (SCAAR).

Unsurprisingly, given these substantial variations in patient characteristics, rates of chronic aspirin treatment as chronic treatment for CAD (unrelated to the index ACS event) varied, between 30% (FAST-MI) and 52.8% (ATACS). Chronic treatment with P2Y12 inhibitors was reported in 7 registries, being highest in ATACS (24.9%).

Pre-hospital use of P2Y12 inhibitors (pre-treatment) was reported in CZECH-2 (14.7% of patients received clopidogrel), FAST-MI 2010 (20% clopidogrel, 1% prasugrel), SCAAR (48.9% clopidogrel, 0.6% prasugrel, 16.8% ticagrelor) and SPUM (14.5% clopidogrel, 0.5% prasugrel, 0.4% ticagrelor).

In hospital, almost all patients received loading doses of P2Y12 inhibitors for the treatment of the index NTE-ACS event. Switching between drugs, mostly reported from clopidogrel to prasugrel, was not frequent (for the named switch from 0% in AAPCI to 11% in FAST-MI).

Time from first medical contact to PCI was reported in five registries, ranging from 4.6 hours (AAPCI/ADAPT) to 27.4 hours (FAST-MI 2010). The great majority of patients received coronary angiography (66% in CZECH-2, 79.6% in DIOCLES, and 100% in AAPCI and ATACS, the latter

being related to the inclusion criteria), and a substantial proportion received PCI (47% in CZECH-2 to 98.4% in SPUM (the latter being again rather high, mostly related to inclusion criteria). Where reported, radial access for PCI varied between 26.5% (ATACS) to 81-83% (Newcastle).

Outcomes

For various effectiveness and safety outcomes, event rates are presented descriptively for the NSTE-ACS cohort in total (Table 2) and by P2Y12 inhibitor (Table 3). Further, they are plotted against mean age of the patients in the various registries (Figure 1).

Ischaemic outcomes

All-cause death rates were from 0.76% (Newcastle 2012) to 4.79% (CZECH-2) in-hospital based on data from 84053 patients for this time point; from 1.61% (SPUM) to 6.65% (CZECH-2) at 30 days; from 3.66% (SCAAR) to 7.16% (DIOCLES) at 180 days, and from 3.14% (AMIS Plus) to 9.73% (FAST-MI 2010) at 1 year.

Cardiovascular death rates were only reported in 2 registries: they were 0.97% (SPUM) and 1.28% (AMIS-Plus) in-hospital; 1.5% at 30 days (data from SPUM only); and 3.25% (data from SPUM only) at 1 year.

For cardiovascular non-fatal ischaemic events, rates were 0.6% (AAPCI/ADAPT) and 2.04% (SPUM) in-hospital, 2.26% (SPUM data only) at 30 days, and 4.23% (AMIS-Plus) and 9.63% (SPUM) at 1 year.

Stroke events were reported in all registries with the exception of the Newcastle registry. They ranged from 0% (CZECH-2) to 0.79% (DIOCLES) in-hospital. Post-discharge stroke events ranged from 0.18% (CZECH-2) to 1.13% (BLITZ-4) at 30 days; were 0.98% (SCAAR) and 1.11% (DIOCLES) at 180 days; and 1.19% (SPUM) and 1.52% (SCAAR) at 1 year.

Recurrent in-hospital MI reported by eight registries ranged between 0.18% (ATACS) and DIOCLES (2.77%). After discharge, the recurrent MI rate was between 0.72% (BLITZ-4) and 5.43% (SCAAR) at 30 days; 3.96% (DIOCLES) and 8.28% (SCAAR) at 180 days; and 3.55% (AMIS Plus) and 9.78% (SCAAR) at 1 year (no 1-year data from other registries were available).

Repeat PCI rates varied widely, between 0.17% (CZECH-2) and 8.3% (AAPCI/ADAPT) in-hospital; 1.29% at 30 days (SPUM, no data from other registries available); and 5.74% at 1 year (SPUM, no data from other registries available). No data for repeated PCI were available at 180 days from any registry.

Outcomes by DAPT

Efficacy endpoints for the analyses are displayed in Figures 1 to 3. Data from 3,199 patients on prasugrel, 36,336 on clopidogrel, and 11,906 on ticagrelor were available for the analysis of all-cause death in hospital.

The univariate analyses showed that patients on prasugrel besides being younger also had lower event rates compared with those on ticagrelor and, to an even greater extent, those on clopidogrel.

The named figures in this manuscript and additional 28 bubble plot graphs in the online supplement display the various ischaemic outcomes at the different time points.

Bleeding

The studies used various bleeding definitions: AAPCI, CZECH-2, and FAST-MI used the definition of TIMI,[18] and since 2012, AMIS-Plus used BARC.[19] ATACS used the definition of GUSTO,[20] and the other registries used unspecified or proprietary definitions as displayed in Table 1. Overall, the data on the various bleeding types and documentation time points were less complete than the data on ischaemic outcomes. FAST-MI 2010, SPUM and SCAAR were the only registries to report various degrees of bleeding (Table 2 and 3, bottom), and SPUM was the only registry that reported bleeding event rates beyond the hospitalization phase.

Data on fatal/life-threatening bleeding during hospitalization were available from four studies (AMIS-Plus, SCAAR, SPUM, and FAST-MI 2010, Figure 4). Rates during this in-hospital time frame fell within a narrow range, between 0% (FAST-MI 2010 and SPUM) and 0.02% (AMIS Plus). At 30 days post-discharge, the rate in SPUM (the only study with data for this time frame) was 0.11%, and at one year, 2.06% (data from SPUM only; no data at 180 days).

For major bleeding events, the database was richer. Seven studies reported major bleeding events in-hospital, which occurred in up 2.77% of patients (DIOCLES). Rates at 30 days post-discharge were available from only two studies (0% in SPUM and 1.08% in CZECH-2). One-year data were available only for SPUM; the rate was 2.06%.

Minor bleeding events were reported in two studies for the in-hospital period. The minor bleeding rates during this period were 0.21% (SPUM) and 2.27% (FAST-MI 2010). At 30 days, the rate was 0.21% (SPUM) and at 1 year it was 4.44% (SPUM, no data from other studies were available).

Outcomes by DAPT

Bleeding event patterns were inconsistent across registries for the three P2Y12 inhibitors in the incidence of bleeding rates for fatal/life-threatening, major, or minor bleeding in hospital in the univariate analyses. While in AAPCI/ADAPT the major bleeding rates were highest for prasugrel (2.16%) and lowest for clopidogrel (1.22%), the opposite was found in SCAAR (prasugrel 0.45% vs. clopidogrel 0.94%). In ATACS major bleeding rates were higher for clopidogrel compared with prasugrel (1.03% vs. 0.63%).

Figure 3 (forest plot) and additional bubble plot graphs in the online supplement display the various bleeding outcomes at different time points.

DISCUSSION

The main results of this contemporary review on the characteristics and outcomes of patients with NSTE-ACS treated with DAPT were in line with those for the STEMI cohort:[3] Overall the rates for death, various other ischaemic outcomes as well as bleeding events were similar or somewhat higher, respectively, compared with the phase III studies of the various P2Y12 inhibitors. There were important differences in the use and patient selection between clopidogrel, prasugrel and ticagrelor, which were associated with differences in ischaemic outcomes. No clear pattern across studies emerged for the P2Y12 receptor inhibitors with regard to bleeding rates for fatal/life-threatening, major, or minor bleeding in hospital.

All registries documented patients on clopidogrel, because the drug has been in use for 15 years for PCI, as well as data on prasugrel (only in DIOCLES numbers were too low for robust analyses and thus are not reported here). Ticagrelor, as it was introduced into clinical practice most recently, was only documented in a limited number of registries (in AAPCI, AMIS-Plus, and SCAAR).

Use of P2Y12 receptor inhibitors in certain patient groups

The baseline characteristics of patients in the various registries suggest that the prescribing information for individual P2Y12 inhibitors is closely followed. Prasugrel was predominantly used in younger patients as compared to ticagrelor, and the oldest population was noted for clopidogrel.

Age is a central factor in the major cardiovascular risk equations such as the TIMI or GRACE scores and is closely related to ischaemic and bleeding events in patients with NSTE-ACS. [21, 22] As younger patients have less comorbidities, and are generally less ill or at lower cardio-vascular risk, respectively, outcomes in the P2Y12 inhibitor subgroups have to be interpreted with great caution if not adjusted for age. Against this background, the PIRAEUS data can be used to obtain a general overview on the current treatment approaches for NSTE in Europe and comparative data *within* the three DAPT regimens, but not *between* regimens.

According to the product labelling, ticagrelor should be used with caution in patients with a history of asthma and/or COPD (due to a relatively high incidence of dyspnoea) and also in patients with renal impairment (due to creatinine level increases).[23] These side effects have not been systematically assessed in the registries contributing to PIRAEUS.

Prasugrel also has a restricted labelling as it is contraindicated in patients with prior TIA or stroke. The drug is generally not recommended in elderly patients (≥75 years), however, following individual benefit/risk evaluation, if treatment is considered necessary, a maintenance dose of 5 mg should be used after a 60 mg loading dose. Further, in patients with low body weight (<60 kg) the 5 mg maintenance dose should be used.[24]

Probably owing to these restrictions of the two newer P2Y12 receptor antagonists, clopidogrel was given to the older and sicker population, despite the fact that the ESC NSTE-ACS guidelines overall give preference to prasugrel and ticagrelor.[7] The current ESC guidelines provide no recommendation for or against pre-treatment with ticagrelor or clopidogrel, as the optimal timing of administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated to date with ticagrelor and clopidogrel. Based on the ACCOAST results, pre-treatment with prasugrel is not recommended.[1] In ACCOAST, prasugrel *given at the time of PCI vs* given as pretreatment resulted in reduced bleeding complications while anti-ischaemic efficacy was preserved.[25]

Event rates overall

An obvious finding across the NSTE-ACS cohorts in the described registries was that the event rates shortly after the ACS event, irrespective of event type, were lower compared to the STEMI cohorts in the same registries (STEMI data were reported elsewhere[2, 3]). For example while all-cause mortality in hospital in STEMI patients was 5.68% in AAPCI, 4.15% in AMIS-Plus, 5.16% in SCAAR and 2.01% in SPUM, the corresponding rates in NSTE-ACS patients were 2.8% in AAPCI, 2.41% in AMIS-Plus, 1.15% in SCAAR and 0.97% in SPUM. This pattern was consistent across studies for the other ischaemic event types and the bleeding events. At 1-year follow up, the all-cause death rates in FAST-MI in STEMI patients were lower than in NSTE-ACS patients (7.13% vs. 9.73%), but not in SCAAR (9.58% vs. 5.26%) or SPUM (4.89% vs. 4.55%). In SPUM, the only registry that provided data for all ischaemic and bleeding endpoints, overall the event rates in STEMI patients at 1 year did not deviate much from those of the NSTE-ACS patients.

Between registries, differences in reported outcomes were profound. The range of all-cause mortality in the in-hospital period varied widely between 0.76% in Newcastle 2012 and 4.79% in CZECH-2, suggesting a selection bias in some registries. Stroke rates in hospital were in a closer range between 0% in CZECH-2 and 0.79% in DIOCLES, but for repeat PCI the differences were enormous between 0.17% in CZECH-2 and 8.3% in AAPCI. The latter endpoint depends on

the setting and the clinical decision rules of the respective centre and is therefore investigator-driven. The CZECH-2 registry differs from most other registries in that there was no centre or patient exclusion (all hospitals participated and documented all eligible patients); thus also patients admitted to resuscitation units or to small community hospitals without availability of a cardiologist were included, what might contribute to the higher event rates.

Overall across all analysed registries, in-hospital and follow-up mortality rates associated with NSTE-ACS treated with PCI were similar or somewhat higher compared with the rates observed in the Phase III studies such as TRITON-TIMI 38 and PLATO for the individual drugs (these trials report on 15 and 12 months (TRITON) or 12 months (PLATO) outcomes respectively, which are not available in most registries, so comparisons are difficult). This finding could be explained by the inclusion of consecutive (less selected) and thus more ill patients in registries as compared to clinical trials.

Bleeding events

Bleeding events were not standardized across registries, and in some registries the definitions were not given. Indeed there is a lack of uniformity in bleeding definitions and the timing of reporting among recent ACS and PCI clinical trials and registries,[19] and uncritical comparisons of the absolute bleeding rates may be misleading in the interpretation of the safety of the various P2Y12 antagonists. Quinlan et al. listed as factors that explain most of the variability in reported bleedings rates the different definitions of major bleeding, the timing of reporting the primary outcome of major bleeding, and the rates of CABG surgery.[26] They illustrated this by comparing the bleeding rates in randomized studies on high dose clopidogrel (CURRENT 2010), on prasugrel (TRITON TIMI-38) and on ticagrelor (PLATO) using the same bleeding definition (i.e. TIMI major bleeding) at the same points in time. When restricting the time period to the first 30 days after the ACS event, a time point where this information was available for all 3 trials, the TIMI major bleeding rates were 1.0% for prasugrel (vs. 0.9% clopidogrel) in TRITON-TIMI 38, 1.4% for ticagrelor (vs. 1.0% clopidogrel) in PLATO and 0.9% for high dose clopidogrel (vs. 0.6%) in CURRENT 2010. [26]

In the registries analysed here, major bleeding rate (in hospital) was lower on prasugrel compared to ticagrelor in SCAAR but conversely higher in AAPCI/ADAPT. In contrast to the findings in AAPCI/ADAPT, in the ATACS, SCAAR and SPUM registries, bleeding rates in the clopidogrel group were higher compared to the newer P2Y12 receptor inhibitors. The latter finding is in contrast to all major randomized studies that contained comparisons between

clopidogrel and the newer P2Y12 receptor inhibitors and is most likely explained by patient selection (older, more comorbid patients on clopidogrel). [26]

Limitations

There were substantial differences between registries in terms of study setting, eligibility of patients, site selection and definition of endpoints including bleeding events, which limits the comparability of results. We did not formally assess nor adjust or weigh the risk of bias in the various observational studies (transfer of raw data was not possible due to data protection). Not all of the previously identified suitable registries[2] provided data in the agreed structured format which could therefore not be analysed for the purpose of this paper. Data were not differentiated between NSTEMI and UA, and some registries were limited to NSTEMI. Lost-to-follow-up rates in most registries were high after 30 days follow-up. The statistical handling of such data sets is challenging, as a conservative approach (all lost-to-follow-up cases counted as affected by an event) will dramatically overestimate the incidence of rare events (such as fatal bleeding or death), while another approach that restricts the analysis to those patients who can be followed (alive and able to report events reliably) will underestimate the true event rates.

Conclusions

PIRAEUS provides a comprehensive picture about the actual outcomes of NSTE-ACS patients as they are currently treated under real-life conditions, and thus complements the data of the randomised controlled phase III trials (RCTs) of the various P2Y12 receptor inhibitors. Overall, in the registries death rates and various other ischaemic outcomes as well as bleeding events were similar or somewhat higher than in the RCTs. This may reflect the fact that consecutive and more ill patients were included in the registries.

Notably, the registries that provided information about NSTE-ACS and UA patients showed considerable differences in setting, patient and treatment selection. The ischaemic outcomes for the three P2Y12 inhibitors differed enormously between registries, most likely driven by the differences in patients' baseline characteristics. Interpretation of bleeding rates is difficult given the differences between registries, among others, in definitions, CABG-related interventions, and femoral/radial access rates.

It is an important learning from PIREAUS that in future registries data collection should be performed in a more standardized way with respect to endpoints, definitions, and time points, to enable further robust common analyses.

Figure legends

Figure 1. The column on the left displays the endpoints and the registries with available data in the NSTE-ACS cohort for the respective endpoint at the end of hospitalisation period. The column “Events/N” shows the number of events and the number of patients in the NSTE-ACS cohort (denominator). The column “Event rate (95% confidence interval)” provides the underlying data for the graph. Boxes in the graph visualise the event rate, the horizontal lines the 95% confidence intervals.

Figures 2 and 3. The graphs show the unadjusted event rate (%) on the y-axis and the mean patient age on the x-axis. Each bubble represents a P2Y12 group (green = prasugrel, blue = clopidogrel, pink= ticagrelor) of the named registry, and the size of the bubbles visualise the patient number of the P2Y12 group. The patient number of each treatment group and further demographic and treatment information is shown in Online Table 1. In the analysis by DAPT group, patients in the ticagrelor group were substantially older than those in the prasugrel group, and those in the clopidogrel group were even older.

Figure 4. The column on the left displays the endpoints and the registries with available data in the NSTE-ACS cohort for the respective endpoint at the end of hospitalisation period. The column “Events/N” shows the number of events and the number of patients in the NSTE-ACS cohort (denominator). The column “Event rate (95% confidence interval)” provides the underlying data for the graph. Boxes in the graph visualise the event rate, the horizontal lines the 95% confidence intervals.

Table 1. Baseline characteristics in the NSTE-ACS cohorts of the various registries

Registry acronym	AAPCI / ADAPT	AMIS Plus	ATACS	BLITZ-4	CZECH-2	DIOCLES	FAST-MI 2010
Patient number (n)	2181	5880	6777	5852	586	1769	1805
Definition of (major) bleeding	TIMI	BARC (since 2012)	GUSTO			fatal, intracranial or requiring surgery or blood transfusion	
CHARACTERISTICS OF PATIENTS							
Age, mean (SD)	65 (13)	66.6 (12.5)	68.8 (12.0)	F 74 (11), M 68 (12)	70 (11)	69 (12)	68 (13.6)
> 75 years, %	23	29.1	34.7			33.2	37.5
Gender, males/females, %	68/32	75/25	70/30	66.6/33.4	65/35	73/27	70/30
Diabetes mellitus, %	22	22.4	33.7	30.6	40.5	34.8	26
Chronic (congestive) heart failure, %		2.6			0	7.9	7
Atrial fibrillation, %	8	4.4	19.6		14.5		8
Coronary artery disease (CAD, CHD), %		38.8	100			35.1	36
Previous stroke, %	7	6.4	7.8		9.2	7.9 (stroke, TIA)	4
Previous myocardial infarction (STEMI/NSTE-ACS), %	17	20.7	28.2	17.3	29.1	27.3	22
Previous PCI, %	22	22.8	35.6	18.7	24.4	22.9	22
Previous CABG, %		8.5	14.2	9.1	12.1	6.5	7
Arterial hypertension, %		67.6	85.9	67.2	76.5	71.2	62
Peripheral arterial disease (PAD), %		6.2	11.5			10.6	12
Current smoking, %	33	35.3	28.9	24.7	25.9	22.8	26
Chronic kidney disease/renal impairment, %		7.2	23.3	11.9		6.4 (severe)	6.5
Antithrombotic pretreatment: Patients on chronic aspirin (ASA), %		47.1	52.8		46.5	48.9	30
Patients on chronic clopidogrel / prasugrel / ticagrelor, %		13 / 0.9 / 1.2	21.5 / 3.4 / 0		9.6 / 0.25 / 0	18.3 / 1 / 0	20 / 0.5 / 0
Patients on oral anticoagulation (VKA or NOAC), %		5			8.1	12.3 (any AC), 8.5 (VKA)	6
ACS characteristics – Killip classes: I / II / III / IV, %	70 / 19 / 5 / 7	87.1 / 8.7 / 2.2 / 1.9	90.3 / 8.7 (II/III) / 1.0	15.1(II) 7.5 (III-IV)	70.9 / 16.3 / 9.1 / 3.6	86.5 / 7.7 / 5.1 / 0.7	80.5 / 11 / 7 / 1

Time from first medical contact to PCI, mean ± SQ or median (IQR) hours	4.6 (2.2 to 11.5)	6.8 (3.0 to 19.0)					27.4 (14.7 to 55)
INTERVENTION DURING INITIAL HOSPITALISATION							
Coronary angiography, %	100	86	100	85.1	66	79.6	91.5
PCI, %	75	81.8	79.3	66.8 (of pts with angio)	47	50.6	66
CABG, %	6	2.7	3.3	13.4 (of pts with angio)		3.6	5
PCI access radial/ femoral, %	46/54	34/66	26.5			77/23	66/22
Repeat revascularization during same hospital stay, %	8	n.r.	4.3		0.2		9
TREATMENT							
I) Pre-hospital pre-treatment for ACS							
Patients with available data at this time point, n	2181						-
Clopidogrel, % overall	29				14.7		20
,loading dose was given in …. %	100						86
Prasugrel, % overall	5						1
,loading dose was given in …. %	100						89.5
Ticagrelor, % overall	24						0
,loading dose was given in …. %	100						0
Aspirin (ASA), %	97				46		28
GPIIb/IIIa inhibitors, %	0						0.2
Unfractionated heparin (UFH), %	52				15		9
Low molecular weight heparin (LMWH), %	31				8		13
Fondaparinux, %	2						1
II) Treatment in hospital							
Patients with available data at this time point, n	2181	5880	6777			1760	-
Clopidogrel , % overall	14	61.5	81.2			88.8	93
, loading dose was given in …. %	98		65.3			68.9	71.5
Prasugrel, % overall	4	15.7	20.9			3.3	18

, loading dose was given in …. %	95				16.6						46.3		28	
Ticagrelor, % overall	13		43.4								0		0	
, loading dose was given in …. %	97										0		0	
Switching from clopidogrel to prasugrel, %	0		7.5		1.9								11	
Switching from clopidogrel to ticagrelor, %	1		8.1								0		0	
Switching from ticagrelor/prasugrel to clopidogrel, %	0		7.3		0.7						-		13	
Aspirin (ASA), %	-		97.2		100						97.4		99	
GPIIb/IIIa inhibitors, %	0		9.2		11.4						4.5		25	
Unfractionated heparin, %			68.6		94.9						8.1		50.5	
Low molecular weight heparin, %			25.6		6.4						82.2		63.5	
Fondaparinux, %			5.3		7.2						8.4		19	
III) Information on treatment at hospital discharge (D)/ after hospital discharge (after)	D	after	D	after	D	after		D	after	D	after	D	after	
Patients with available data at these 2 time points, n			5291		6777			549	484	1716		1749		
Clopidogrel treatment at discharge/after discharge, %			55.1		73.6			70	27	67.2		68		
Prasugrel treatment at discharge / after discharge, %			17.7		17.8			0.7	0	4.3		16		
Ticagrelor treatment at discharge / after discharge, %			27.1					1.1	1.2	0		0		

Registry acronym	**Newcastle 2010**	**Newcastle 2011**	**Newcastle 2012**	**Newcastle 2013**	**SCAAR**	**SPUM**
Patient number (n)	1356	1578	1445	1575	52319	931
Definition of (major) bleeding					Study specific	
CHARACTERISTICS OF PATIENTS						
Age, mean (SD)	65.8 (12.7)	65.6 (12.8)	65.7 (13)	65.9 (12.7)	68 (11)	65 (12.3)
> 75 years, %	34.4	33.4	37.4	32.9	28.6	24.9
Gender, males/females, %	68/32	68/32	66/34	67/33	68/32	77/23
Diabetes mellitus, %	18.9	19.5	22.8	25.1	25.2	21.6
Chronic (congestive) heart failure, %					10.8	2.6

Atrial fibrillation, %					8.2	
Coronary artery disease (CAD, CHD), %					28.6	
Previous stroke, %	8	7.3	8.37	7.4	9.4	2.7
Previous myocardial infarction (STEMI/NSTE-ACS), %	28.8	26.5	30.2	27.6	24.2	20.5
Previous PCI, %	15.9	16	17.7	20.8	15.5	21.8
Previous CABG, %	6.9	7	8.7	7.1	9.5	8.3
Arterial hypertension, %					56.8	65.7
Peripheral arterial disease (PAD), %	5.8	6.1	7.7	8.4	5.2	8.6
Current smoking, %	24.3	21.5	21.5	20.3	21	36.6
Chronic kidney disease/renal impairment, %	3.1	3.7	4	6.2	21.4	0.9
Antithrombotic pretreatment: Patients on chronic aspirin (ASA), %					37.8	42
Patients on chronic clopidogrel / prasugrel / ticagrelor, %					5.7 / 0 / 0.3	14.5 / 0.5 / 0.4
Patients on oral anticoagulation (VKA or NOAC), %					5.3	3.9
ACS characteristics – Killip classes: I / II / III / IV, %					58.2 / 1.8 / 0.5 / 0.3	87.8 / 8.4 / 2 / 0.8
Time from first medical contact to PCI, mean ± SQ or median (IQR), hours					10.5 (8.0)	6.2
INTERVENTION DURING INITIAL HOSPITALISATION						
Coronary angiography, %	86.5	90.6	84.2	86.8	100	100
PCI, %	71.5	63.6	63	66.3	67.5	98.4
CABG, %					6.9	1.6
PCI access radial/femoral, %	82/18	83/17	82/18	81/19	66/34	
Repeat revascularization during same hospital stay, %	0.8	0.7	0.7	0.9	0.7	0
TREATMENT						
I) Pre-hospital treatment for ACS						
Patients with available data at this time point, n					52319	927
Clopidogrel, % overall					48.9	14.5
, loading dose was given in …. %						
Prasugrel, % overall					0.6	0.5
, loading dose was given in …. %						
Ticagrelor, % overall					16.8	0.4

, loading dose was given in …. %												
Aspirin (ASA), %											67	42
GPIIb/IIIa inhibitors, %											0.5	
Unfractionated heparin (UFH), %											3	
Low molecular weight heparin (LMWH), %											4.7	
Fondaparinux, %											35.1	
II) Treatment in hospital												
Patients with available data at this time point, n	1827		1948		1945		1972		52319		926	
Clopidogrel , % overall											1.9	76.8
, loading dose was given in …. %	64.1		67.7		65.7		55.9				66	
Prasugrel, % overall											1.2	8.5
, loading dose was given in …. %	35.7		32.3		34.2		29.8				6	
Ticagrelor, % overall											1.5	9.5
, loading dose was given in …. %	0.05		0		0.05		14.3				9.2	
Switching from clopidogrel to prasugrel, %											1.7	0.5
Switching from clopidogrel to ticagrelor, %											19.4	2.1
Switching from ticagrelor/prasugrel to clopidogrel, %											3.3	0
Aspirin (ASA), %											1.3	98.5
GPIIb/IIIa inhibitors, %											5.4	19.5
Unfractionated heparin, %	27		21.8		16.9		14.5		56.6		95.2	
Low molecular weight heparin, %	69.4		72.8		78.3		73.7		2		5.6	
Fondaparinux, %	7.1		7.8		12.4		11.4		0.3		5.2	
III) Information on treatment at hospital discharge (D)/ after hospital discharge (after)	D	after	D	after	D	after	D	after	D	after	D	after
Patients with available data at these 2 time points, n	1827		1948		1945		1972		52319		931	
Clopidogrel treatment at discharge/after discharge, %									63		64.1	
Prasugrel treatment at discharge / after discharge, %	64.1		67.7		65.7		55.9		0.9		14.5	
Ticagrelor treatment at discharge / after discharge, %	35.7		32.3		34.2		29.8		19.2		9.8	

F= female; M= male

Table 2. Endpoints in the total NSTE-ACS cohorts

	AAPCI/ ADAPT	AMIS Plus	ATACS	BLITZ-4	CZECH-2	DIOCLES	FAST-MI 2010	Newcastle	Newcastle 2010	Newcastle 2011	Newcastle 2012	Newcastle 2013	SCAAR	SPUM
All-cause death														
in hospital	2.8	2.41	1.65	2.08	4.79	2.94	2.49	1.07	1.18	1.2	0.76	1.14	1.15	0.97
30 days				3.23	6.65	3.66	2.96						1.76	1.61
180 days						7.16							3.66	
1 year		3.14					9.73						5.26	4.55
CV death														
in hospital		1.28												0.97
30 days														1.5
180 days														
1 year														3.25
CV events														
in hospital	0.6													2.04
30 days														2.26
180 days														
1 year		4.23												9.63
Stroke														
in hospital	0.32	0.49	0.21	0.58	0	0.79	0.11							0.21
30 days				1.13	0.18								0.29	0.43
180 days						1.11							0.98	
1 year													1.52	1.19
Recurrent MI														
in hospital	0.28	0.56	0.18	0.97	0.68	2.77	1.27							0.86
30 days				0.72	0.9								5.43	1.07
180 days						3.96							8.28	
1 year		3.55											9.78	3.57
Repeat PCI														

in hospital	8.3		4.31		0.17									0.86
30 days														1.29
180 days														
1 year														5.74
Fatal/life-threating bleeding														
in hospital		0.02					0						0.01	0
30 days														0.11
180 days														
1 year														2.06
Major bleeding														
in hospital	1.56		0.94		0.68	2.77	1.83						0.96	0
30 days					1.08									0
180 days														
1 year														2.06
Minor bleeding														
in hospital							2.27							0.21
30 days														0.21
180 days														
1 year														4.44

Numbers show the incidence rates of various effectiveness and safety (bleeding) outcomes at various time points, in the total NSTE-ACS populations in each study (across treatments).

Empty fields show that the respective parameter has not been collected at this time point in a given registry. No summary statistics across all studies were generated.

Table 3. Endpoints in the NSTE-ACS cohorts by P2Y12 receptor inhibitor based DAPT

	AAPCI/ADAPT			AMIS-Plus			ATACS			DIOCLES			SCAAR			SPUM		
Treatment	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C
All-cause death																		
in hospital	1.08	2.11	2.22	1.64	1.31	3.05	1.18		1.68			2.22	1.24	0.94	0.93			
30 days												3.02	1.46	1.26	1.45	0		1.01
180 days												6.3	2.58	2.57	3.02			
1 year				0.61	2.38	3.72							3.37	3.39	4.5	0		4.22
CV death																		
in hospital				1.06	0.56	1.57												
30 days																0		0.34
180 days																		
1 year				0.61	0	2.05										0		1.86
CV events																		
in hospital	1.08	0.5	0.55													2.22		0.67
30 days																2.96		1.68
180 days																		
1 year																5.93		8.78
Stroke																		
in hospital	0.54	0.37	0.22	0.23	0.44	0.58	0.08		0.24			0.72				0		0.17
30 days													0.22	0.04	0.29	0		0.34
180 days												0.94	0.45	0.27	1.01			
1 year						5.14							1.01	0.4	1.53	0		1.18
Recurrent MI																		
in hospital	0.54	0.12	0.33	0.7	0.37	0.62	0.24		0.17			2.8				2.22		0.34
30 days													6.97	1.64	5.91	2.22		0.5
180 days												4.02	8.76	2.49	9.54			
1 year				6.13	1.85	3.24							11.24	2.98	11.55	1.48		3.04

Repeat PCI																		
in hospital	9.19	8.67	7.98				4.87		4.12							1.48		0.5
30 days																2.22		1.01
180 days																		
1 year																2.96		5.74
Fatal/life-threating bleeding																		
in hospital				0	0.06	0							0	0.02	0	0		0
30 days																0		0
180 days																		
1 year																0		1.52
Major bleeding																		
in hospital	2.16	1.36	1.22				0.63		1.03			2.93	0.45	0.84	0.94	0		0
30 days																0		0
180 days																		
1 year																0.74		1.35
Minor bleeding																		
in hospital																0		0.17
30 days																0		0.17
180 days																		
1 year																2.22		5.07

Numbers show the incidence rates of various effectiveness and safety (bleeding) outcomes at various time points, for prasugrel (P), ticagrelor (T), and clopidogrel (C). Empty fields show that the respective parameter has not been collected at this time point. No summary statistics across all studies were generated.

Figure 1. In-hospital event rates in the various registries in the NSTE-ACS groups

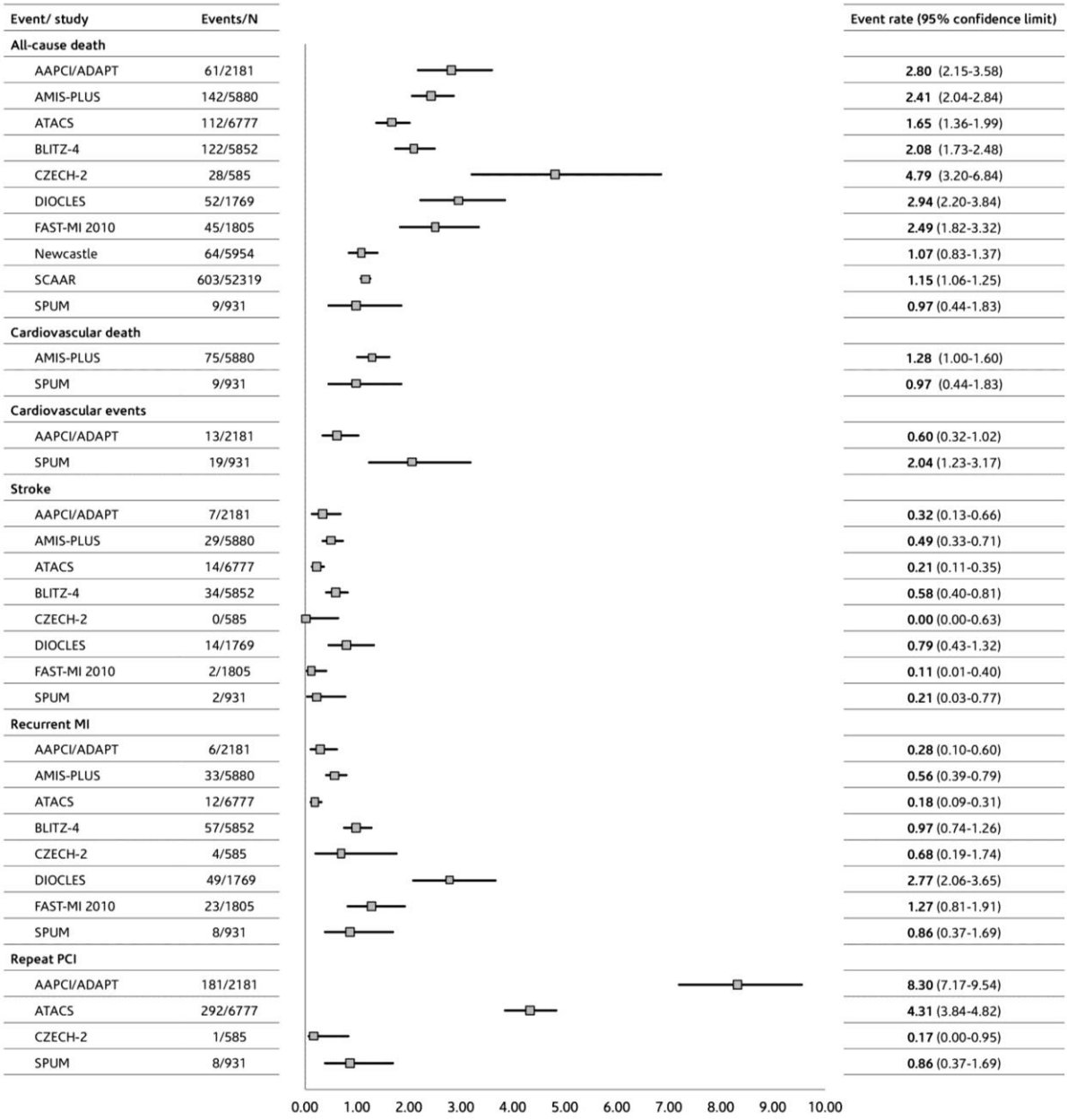
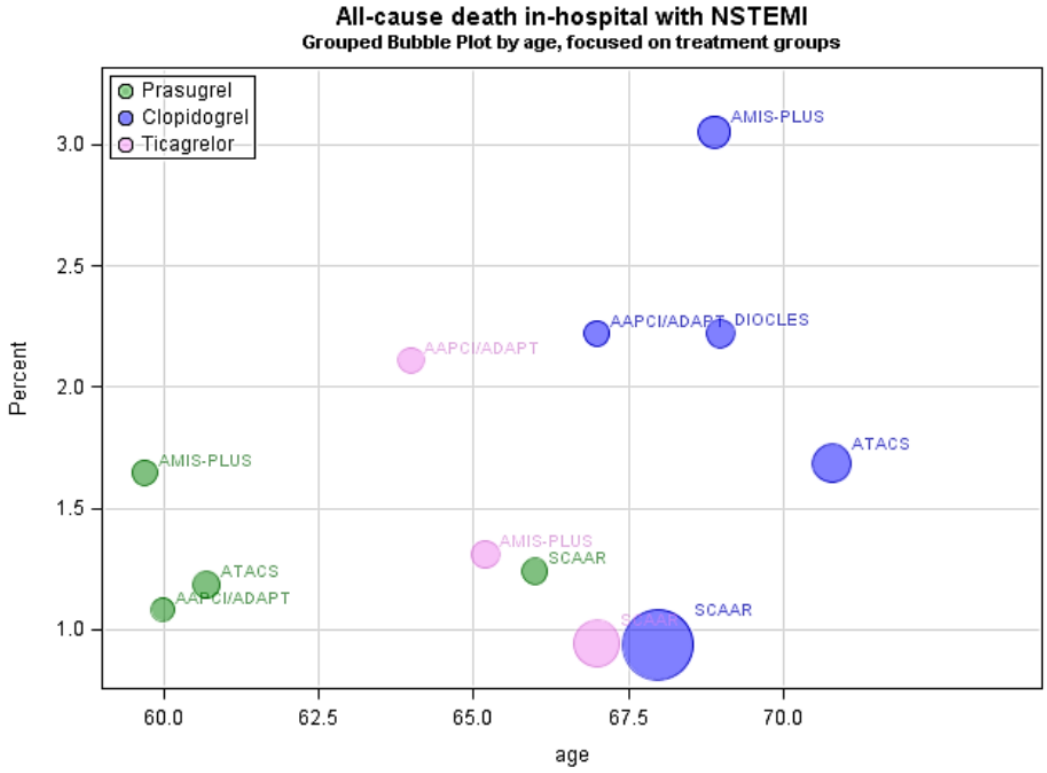


Figure 2. All cause-death in hospital (top) and at 1 year (bottom) in the total NSTE-ACS cohorts, and by P2Y12 receptor inhibitor DAPT treatment



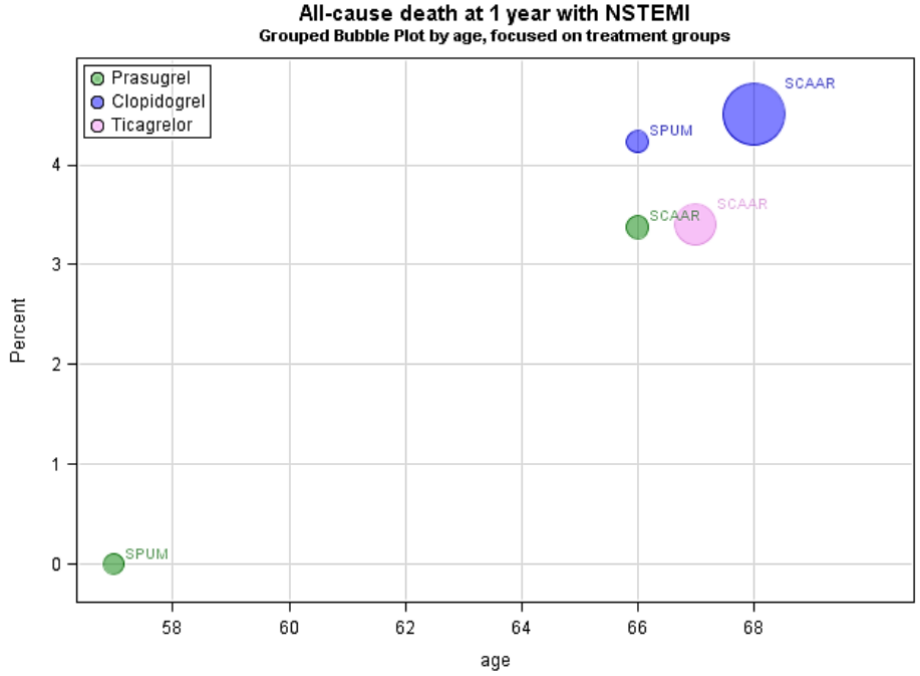


Figure 3. Cardiovascular death in hospital in the total NSTE-ACS cohorts, and by P2Y12 receptor inhibitor DAPT treatment

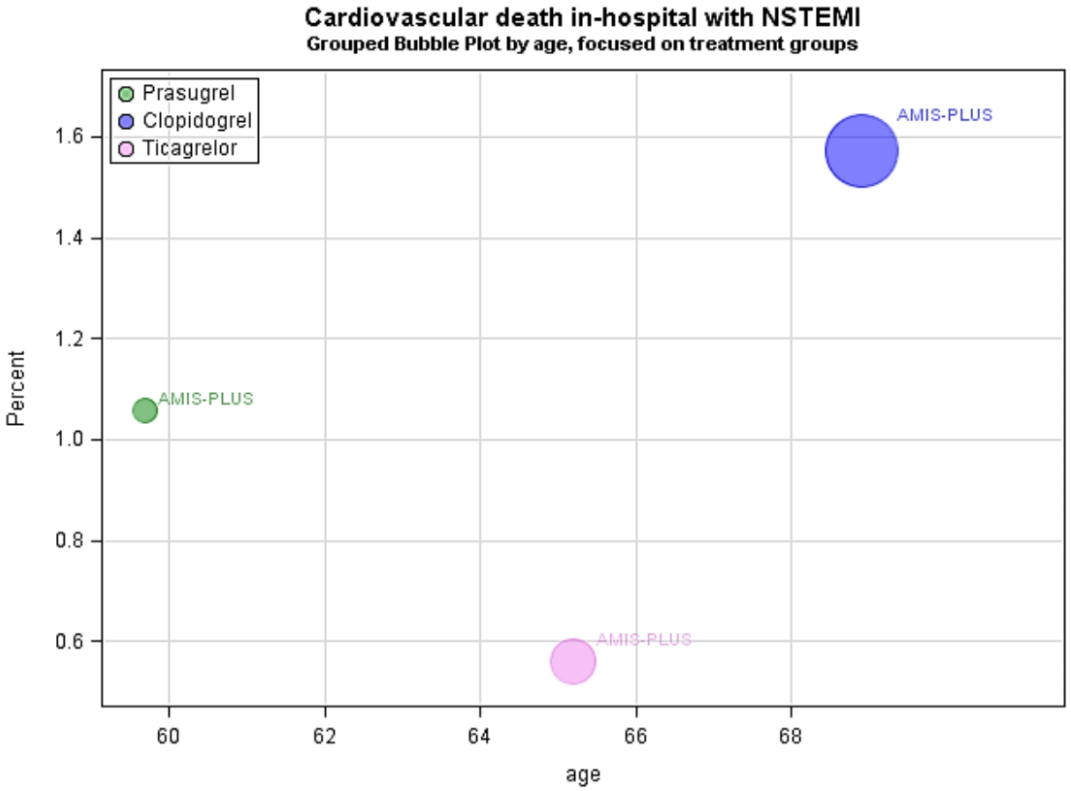
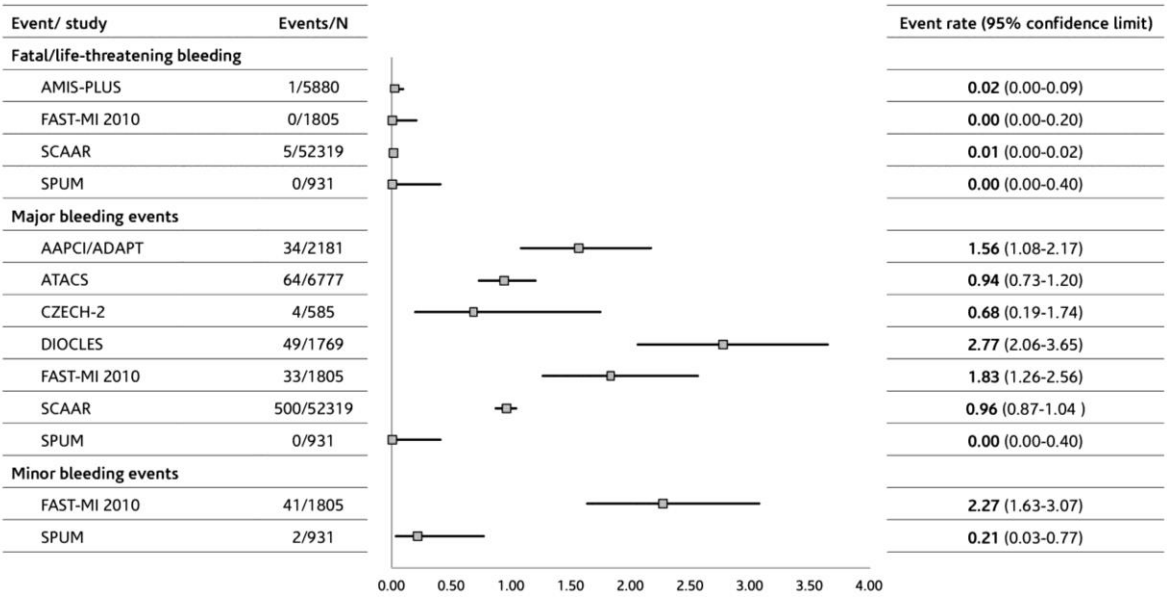


Figure 4. Bleeding rates in hospital in the individual registries in the NSTE-ACS groups



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Disclosures

Pontus Andell
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